IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Sanders et al.	
Application No.: 10/537,280	
Filed: 5/27/2005	Group Art Unit: 1647
Title: Binding Partners for the Thyrotropin Receptor and Uses Thereof	Examiner: C.M. Woodward
Attorney Docket No.: AATH.P-001	Conf. No.: 1845

Declaration Under Rule 132

I, Dr Bernard Rees Smith, declare as follows:

1. I have a degree from the University of Sheffield, UK in the field of chemistry, and also a Doctorate in the field of biological chemistry. I have worked in the autoantibody assay field for 40 years.

2. I am a named inventor of the above-captioned application. As such, I am familiar with the application, including the claims thereof.

3. I am aware that an office action has issued in this case, in which the Examiner asserts that antibodies described by Akamizu et al. and Kohn et al. have the characteristics required by the claims of this application.

4. I understand that the claims will be amended in a submission filed concurrently with this declaration to specifically state that the binding partners for the TSH receptor of the invention have two properties, namely (1) the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor and (2) the characteristics of patient serum TSH receptor autoantibodies with respect to stimulation of cAMP production by cells expressing the TSH receptor.

5. As explained in the present application, patient serum TSH receptor autoantibodies inhibit TSH binding to the TSH receptor. It is clear from Paragraph 0024 of the corrected publication of the application that TSH receptor autoantibodies can be characterized by their ability to inhibit TSH binding to the TSH receptor. This is illustrated in the Examples - paragraphs 0278 and 0300 describe patient sera, and state that sera from patients with Graves' disease of different disease duration showed inhibition of ^{125}I-labeled TSH binding to the TSH receptor. The results shown in Table 5 for the international standard for TSH receptor autoantibodies (NIBSC 90/672) demonstrate that patient autoantibodies inhibit TSH binding to the TSH receptor. Therefore, inhibition of TSH binding is a recognised characteristic of patient autoantibodies.

6. Patient autoantibodies are also known to stimulate cAMP production:

this is a further characteristic of patient autoantibodies. As explained in Paragraph 0003 of the corrected publication of the application, Graves' patient serum TSH receptor autoantibodies bind to the TSH receptor in such a way as to mimic the actions of TSH, ie stimulating the thyroid gland. Patient autoantibodies stimulate the thyroid in the same way that TSH itself does - by binding to the TSH receptor (expressed on the surface of thyroid cells) in such a way as to activate the receptor to exert intracellular effects. Therefore, and as stated in Paragraph 0011 of the corrected publication, patient serum TSH receptor autoantibodies are usually powerful thyroid stimulators (TSH agonists). By "thyroid stimulators", it is meant that the patient serum TSH autoantibodies bind to the TSH receptor and, as a result of this binding, activate adenylate cyclase and thus elicit stimulation of cyclic AMP (cAMP) production. For example, Paragraph 0282 refers to the ability of patient serum autoantibodies to stimulate the production of cAMP in CHO cells expressing human TSH (hTSH) receptor. Table 11 illustrates typical results observed in the stimulation of cAMP with the International reference preparation of thyroid stimulating autoantibodies (NIBSC 90/672). Increased cAMP production is a known property of the International standard for TSH receptor autoantibodies. Therefore it is known that patient serum autoantibodies stimulate cAMP production. Stimulation of cAMP production is thus a characteristic of patient autoantibodies.

7. Akamizu discloses two recombinant monoclonal antibodies to the TSH receptor, (referred to as 101-2 and B6B7). Neither of the Akamizu antibodies have both the characteristics required by the amended claims: the Akamizu antibodies lack one of these characteristics. Although the Akamizu antibodies may have the characteristics of patient serum TSH receptor autoantibodies with respect to stimulation of cAMP production by cells expressing the TSH receptor, the Akimamu antibodies do not have the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor. This is clear from the Akamizu paper itself. For example, the abstract states that "although [the affinities of the Akamizu antibodies] were lower than that of TSH, their binding was not displaced by TSH ... these findings suggest that these antibodies interact with the N-terminal region of the receptor and transduce a signal through binding sites different from TSH". On page 1600, column 1, lines 4 - 5 further state that the "101-2 epitopes in the N-terminal region of the receptor are not related to TSH binding"; the B6B7 binding site is noted to be in the same region as the 101 2 binding site; B6B7 also does not inhibit the binding of TSH to the TSH receptor (page 1600, column 1 lines 22 to column 2 line 2). It is therefore clear that the Akamizu antibodies do not inhibit TSH binding to the TSH receptor. This is explicitly stated by Akamizu on page 1600, column 2 lines 18 to 19: "none of the monoclonal TSAbs exhibited TSH-binding inhibitor activities".

8. Kohn characterizes a number of human monoclonal antibodies to the TSH receptor. However, it is clear from the Kohn article that none of the Kohn antibodies have both the characteristics of patient serum autoantibodies required by the amended claims. Each of the Kohn antibodies lacks at least one of the characteristics required by the amended claims. Kohn discusses 20 antibodies. 12 of these are described as stimulating TSHRAbs, which increase cAMP levels. The remaining 8 are referred to as TSIIs, and these are characterized as inhibiting TSH binding to the receptor. In Kohn, the two characteristics of the antibodies of the present invention are present only separately, in distinct antibody populations (each having only one of the required characteristics), as indicated by the

statement (on page 3999, column 1, lines 30 to 33) that clones were identified which produced Graves' stimulating TSHRAbs or TBIIs. It is explicitly stated on page 4002, column 2 lines 18 to 24 that "none of the clonal stimulating TSHRAbs exhibited significant ability to inhibit TSH binding ... even as a function of the IgG concentration". This is also illustrated in Figure 3, which shows the ability of the Kohn antibodies to inhibit TSH binding to human thyroid membranes. In particular, of the Kohn antibodies which appear to have cAMP-stimulating activity (that is, CM11E5, CM2A7, etc) did not inhibit TSH binding - therefore, these antibodies lack the first characteristic of patient autoantibodies required by claim 121 as amended.

9. Conversely, the TBII antibodies described in Kohn are reported to inhibit TSH binding to the TSH receptor, but these antibodies do not have the characteristics of patient serum TSH receptor autoantibodies with respect to stimulating cAMP production by cells expressing the TSH receptor. This is also stated explicitly by Kohn in the paragraph bridging pages 4002 - 4003: "Eight clones produced TBIIs that inhibited TSH binding to either solubilised porcine thyroid membranes (the commercial TRAK assay) or solubilised membranes from human TSHR transfected CHO cells. None of these increased cAMP levels". This is also illustrated in Figure 3, which shows that the Kohn antibodies which inhibit TSH binding (that is, CM5C3, DT2F1, etc) did not have cAMP-stimulating activity - therefore, these antibodies lack the second characteristic of patient autoantibodies, as set out in amended claim 121.

10. It is therefore apparent from the data presented in the Kohn paper that Kohn describes monoclonal antibodies which either (a) bind to the TSH receptor in such a way as to stimulate the TSH receptor or (b) bind to the TSH receptor in such a way as to inhibit TSH binding. However, none of the antibodies have both characteristics - the antibodies which bind so as to stimulate the TSH receptor do not inhibit TSH binding and, conversely, those antibodies which bind to the TSHR in such a way as to inhibit TSH binding do not stimulate. Therefore, none of the Kohn antibodies have the two characteristics of patient autoantibodies required by the amended claims.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 10th March 2009

Dr Bernard Rees Smith